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Case reports in an evidence-based world

Now that medical practitioners all over the world are firmly convinced that 'evidence' should guide their actions, is there still a role for the age-old cornerstone of the medical literature, the case report? The answer is an emphatic yes: the case report is as necessary as ever for the progress of medical science and the practice of medicine. Nevertheless, confrontation with the evidence-based medicine movement has taught us its proper role.

In classic evidence-based medicine teaching, the case report and the case series are the lowest forms of intellectual life, even lower than the case–control study[1,2]. This hierarchy, with the randomized trial on top, holds for a single purpose—the evaluation of medical interventions with wide applicability in which there is uncertainty about a benefit that is in itself not striking. Case reports and case series have other roles that answer basic needs in medicine.

A taxonomy of case reports and case series

Broadly speaking, there are two categories: one is the progress of medical science, the other is education and quality assurance. They can be refined as follows.

Descriptions of new diseases

There is no other way but a series of cases to bring a potentially new disease to the attention of the medical public. New diseases exist in two varieties[3]. The commonest variety is a further subdivision and refinement of existing entities. A recent example is 'mitochondrial diabetes'—the shrewd observation that in certain families diabetes has a maternal inheritance, and the subsequent discovery of its molecular mitochondrial basis. The disease might be as old as *Homo sapiens sapiens*, whose genome is said to go back 30 000 years, but the maternal inheritance could only strike a clinician who was knowledgeable about mitochondrial disease (a relatively new concept). Once the condition had been 'seen', the description of a handful of cases brought the message to a wider audience; the patients were observed to have fewer vascular and neural complications than those with common-or-garden diabetes; and it became worthwhile to consider this type of diabetes as a separate entity. The second variety is 'truly new' diseases. AIDS stands out as a paradigm. Although the virus may be over one hundred years old in central Africa, the disease was recognized only when it spread by international intercourse. The recognition was by clinicians who were startled by the 'total immunodeficiency' in patients with no apparent reason for immunodeficiency of that type and severity[4,5].

Aetiology and recognition of side effects

Close to the recognition of new diseases stands the recognition of new aetiologies. Side effects are sometimes detected because they produce diseases that were previously non-existent or unrecognized—for example, the eosinophilia myalgia syndrome, specific forms of valvulopathy with slimming drugs, or retrolental fibroplasia. At other times a known disease develops in unusual and unexpected circumstances: a young woman developing venous thrombosis 'out of the blue', i.e. without any true precipitating factors, in the first weeks of taking oral contraceptives; a middle-aged man without known cardiovascular disease who has a myocardial infarction on first trying out the 'erection pill'. Side effects apart, other clues to aetiology can be derived from case reports or case series. The first clues about tobacco smoking and lung cancer came from surgical patient series in the 1920s and 1930s; formal case–control and cohort studies came only decades later[6].

Study of mechanisms

To study disease mechanisms, one patient or just a few may suffice. A new form of thrombophilia was detected by diligent pursuit of the clotting abnormality in one family; it proved to be the most widespread genetic cause of thrombosis[7,8]. In other circumstances, the condition of the patient itself leads to alterations that offer clues to physiological mechanisms. Contrary to prevailing dogma, artificial ventilation with positive end-expiratory pressure in adult respiratory distress syndrome proved most efficient when patients were prone[9,10]. Rumour has it that medical mishaps played a large part in this discovery. When patients on a ventilator were found in the morning to have turned themselves round, they were discovered each time to have better blood gas values. Case reports and series remain necessary for advances of the kind that are often credited to basic science. Most of the recent progress in genetics—e.g. the elucidation of the genetics of cystic fibrosis or of sickle

cell anaemia—is firmly rooted in earlier case studies of physiological mechanisms[11].

Therapy and prognosis

Sometimes the effect of a medical intervention is so surprisingly strong, against the background knowledge of 'usual prognosis', that a case report or case series suffices to convince. That happened with a new therapy for chloroquine poisoning (mechanical ventilation and diazepam plus adrenaline). Ten of eleven patients survived a dose of chloroquine (5 g or more) that was quite securely known to be lethal[12]. Case reports can also give clues about new indications for old drugs. Hypoglycaemia in patients with infections who were treated with sulpha drugs led to the development of oral hypoglycaemics; mood improvement on a tuberculostatic drug led to new antidepressants; and decreased serum cholesterol was observed in schizophrenia patients treated with niacin[13]. The study of prognosis can often be pursued profitably with a case series—as in a series of patients with scleroderma who died of pulmonary fibrosis, a condition that is otherwise rare but fits clinically with the overall derangement of the connective tissue in scleroderma[14].

Education

For medical undergraduate education the use of case vignettes is unsurpassed. One only recognizes what one knows. Since diagnosis rests on pattern recognition, 'knowing' a disease is just a little more than a description in your favourite textbook on your shelf—or even having memorized it by heart as a student (for the older among us). Case presentations during ward rounds and clinicopathological conferences might have their strongest role in postgraduate education—rare presentations, difficult management, rare complications and human tragedies due to the missing of some clue. They also show young physicians 'how to think', that is, how seasoned clinicians think about a particular patient problem. Moreover, by example, they teach how in-depth probing of patient problems leads to renewed thinking about mechanisms and to new scientific questions. How and why ward rounds and clinicopathological conferences work has been described wonderfully by a participant observer[15].

Quality assurance

Case histories do help in implicit and explicit quality assurance—implicitly when the lesson of the clinicopathological conference is 'do not make the same mistake as I did'; explicitly when a series of cases with an unfavourable outcome is collected to see whether that outcome might have been prevented. Such a collection of cases can then be judged by predefined criteria or with a post-hoc informal judgment. A courageous form is the 'lesson of the week', as published in the *British Medical Journal*.

Why do case reports work?

A case-report teaches us what is 'un-known' or 'un-recognized', either what medicine does not yet know ('progress'), or what individual doctors have not yet recognized ('education'). Almost always there is 'the element of surprise'. In the case report that leads to progress in medical scientific knowledge—generally qualified as research—the surprise stems from a comparison with our theoretical expectation. Our expectation is a type of 'mental control group'. We did not expect diabetes to have maternal inheritance, we did not expect the young woman without any risk factors to get venous thrombosis, and we did not expect the young man without any immunosuppressive drugs to develop profound immunosuppression. For side effect detection there is often a double element of surprise. Not only is the disease totally unexpected in this patient, but this is also one of the first occasions on which the physician prescribed this particular drug. Two rare events coinciding is clearly too much, and the side effect gets reported.

According to Karl Popper, this way of discovering new ideas fits his hypothetico-deductive model[16]. The hypothesis is our (vaguely stated, and often not very explicit) theoretical conjecture; the negation is the observation that strikes us—because it runs counter to the conjecture—and therefore we are forced into new theorizing. To other observers of medical science, however, case series are examples of observations leading immediately to new scientific ideas, and therefore they are the last resort of inductionism[17]. Whatever your philosophical preferences, they work.

The meaning of 'expectation', in discussing how observations strike us, also differs for different commentators. In the above, we used theoretical expectation almost in the epidemiological sense—what one would have expected from a control group. Others, however, speak of Pasteur's sense—'Chance favours only the prepared mind'[18]. They will maintain that Fleming immediately saw that the mould was doing something exciting to his culture on the window sill *because* he was constantly on the outlook for substances that would inhibit bacterial growth. Both expectations are sides of the same coin: they help to explain why someone suddenly gets an idea when confronted passively with an observation.

'Conjectures and refutations'

As seen in the chloroquine example and in mechanism examples, case reports and series are sometimes actively pursued because of specific expectations. Recently,

Charlton and Walston wondered whether this use of case series might be formalized[18]. I cannot do justice here to the depth of their argument, but their suggestion is that, after the proposal of a new theory, one might go back to collect existing cases, either from the published work or from medical practice, to see whether they fit the new theory or not. Were certain things mentioned at a time that the new theory was not yet known? Can new evidence be elicited from the old cases that tells us something about the chances of the theory being true?

This idea makes sound sense. There is the highly debated question whether oral contraceptives that contain gestodene or desogestrel as progestins increase the risk of venous thrombosis. For deep venous thrombosis of the legs, the issue is settled, at least for epidemiologists who have looked at all sides of the argument[19,20]. As an aside to a larger case–control study in the Netherlands, a clear association was also found with venous thrombosis of the cerebral sinuses[21]. This was not confirmed in Italy[22]. The difficulty with studies on new patients is that the population use of these contraceptives has strongly increased over time. I was therefore tempted to go further back in the published work, to see whether older studies on cerebral sinus thrombosis could give any clue—preferably studies that were performed and published before 1995, when the controversy had not yet arisen and these oral contraceptives had not swamped the market. I found one case series that was informative—a Swiss series of five consecutive young women who had been admitted with cerebral sinus thrombosis between 1988 and 1990 and who were all using oral contraceptives. Four of the five had used a contraceptive with desogestrel or gestodene[23]. Though far from constituting 'proof' in an area as hotly contested as this one, it nevertheless confirms Charlton and Walston's idea of the usefulness of going back to existing cases with a firm hypothesis in mind.

Can case reports convince on their own?

Of course they can. As regards mechanisms, medical practitioners are well accustomed to generalizing from a few patients with the same disease. Mechanisms need only be studied in a handful of patients; the patients need not be representative, except for the type of disease in question. After all, we rarely hesitate to generalize from the squid giant axon or the frog heart to their human counterparts; to go from a few patients to many is a much smaller step. This is true for general pathophysiology on the level of systems, e.g. discovering autonomic dysfunction in patients with diabetes. It also holds for the latest ventures in genetics where mutations are discovered in individual patients and the relation between the mutation and the cellular derangement is studied in the same patients.

But can they also lead to action? In the area of side effects, they certainly can. Remember the unexpected sudden deaths during or immediately after intravenous infusion of high dosages of an anti-emetic[24]. A few such deaths, reported independently by physicians who saw no reason at all for the sudden intractable arrhythmias in their cancer patients, sufficed to alarm the authorities. The intravenous form was withdrawn from the market.

Also when the effect is beneficial and intended, case reports or case series can be sufficient, as in the chloroquine example. However, there is the risk of a 'random high'. Pocock and Hughes described why randomized trials that are stopped prematurely because of extremely high benefit (i.e. much larger than expected) will more often than not be on a 'random high'; the direction of the effect is true, the magnitude is indeed large, but there is the distinct possibility that in this particular instance mere chance added an extra benefit that made it so striking as to stop the trial[25]. In the next trial the effect will still be there, but may be just a trifle less than in the trial that was stopped prematurely (similar to a 'regression to the mean' phenomenon). The case series of a new treatment for severe chloroquine poisoning, enthusiastically published in a top journal[12], might be an instance of the same phenomenon. Readers do not doubt that, next time they encounter such a patient, they will apply this treatment. Nevertheless, they know that the published literature is always somewhat optimistic, and it might have been a lucky day that landed the authors and the patients in the high-ranking journal. The same caution goes for side effects. Side effects will only strike when seen rather abundantly within a short period of time. So, the report that OKT3 antibody treatment in a series of transplantation patients induced a surprising number of lymphoreticular disorders, early in therapy, will certainly contain truth, but the magnitude of the effect might reflect bad luck in these patients[26]. This leads to an intriguing paradox: on the one hand, we only 'see' the effect because of the fortuitous 'random high', and thereby we discover a truth; on the other hand, the magnitude of the effect is almost certainly overestimated, and therefore not true.

Ethical aspects

Case reports have taken a battering from the newest waves in medical ethics, concerning patient privacy and autonomy[27]. Not only is informed consent held to be mandatory for publication, but everything that is recognizable in a case report and all 'unnecessary information' should be deleted. As regards informed consent, there is the grave dilemma whether the whims of an individual should obstruct transmission of information that might be of benefit to other patients[28]. Attempts at removing 'everything recognizable' are essentially futile. We all recognize the

current US President or UK Prime Minister, even with black bars over the eyes. Friends and relatives will recognize a patient not only from pictures but also from descriptions. And what constitutes unnecessary information? The information in an old case report that a patient had been a sailor turned out to be not-unnecessary when that patient was deemed retrospectively to have had AIDS[29]. Deliberate fabrication is sometimes advocated. Just imagine if the occupation of that patient had been changed to solicitor or notary public.

What makes a good case report?

Now that leading journals have rediscovered case reports[30], there remains the question, for authors, reviewers and readers alike, what is a good case report? The days of droning out one case after the other, as an excuse for a haphazard literature review, are over. Evidence-based medicine has finished all that, mercifully. The purpose of a good case report is specifically to make your point. What point you make will depend on the type of report—student education, postgraduate education, therapy, prognosis, aetiology. The greatest challenge of a case-report is that it should convince on its own. It should bring a general truth that can be stated in abstract scientific terms but nevertheless be based on a single observation or a handful of observations. Besides clearly formulating the point you want to make, you should preferably also specify the strong prior expectation that forms the basis of your report. That will make it obvious to the readers why they should be surprised. The expectation can be a 'mental control group', based on theory, or on the shared experience of physicians, or it can be derived from the published work. In sum: know securely what point you want to make, make only one and be brief.

Conclusion: the role of case reports

Principles of evidence-based medicine rank the randomized trial on top for strength of evidence. That is fine for undertakings that are mainly confirmatory, bring a final quantification, but offer little scientific novelty in themselves. Before an idea can be confirmed or quantified, it has first to be discovered. For true intellectual advancement, i.e. in proposing new problems, new solutions, or new ideas, the hierarchy is of necessity reversed. Solidly on top sits the case report and case series—observations of first cases, of mechanisms, of aetiological or therapeutic surprises. Case reports and case series do not provide evidence with the same strength as more formal clinical or laboratory research. They are highly sensitive in picking up novelty in a qualitative way but poorly specific as to quantitative confirmation. Randomized trials have maximal procedural guarantees against all kinds of biases; for that very reason, they are not set up for discovery. Case reports and series have large potential to stimulate new learning, but lack such safeguards. There is no other way to detect new ideas, however. Without new ideas all advancement in medicine would cease. It is the 'discovery' aspect, both scientific and educational, that makes case reports and series such great fun to read, to discuss and to present. In the age of evidence-based medicine, they remain as necessary as ever.

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